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A pilot study of lower extremity lymphedema, lower extremity function, and quality of life in women after minimally invasive endometrial cancer staging surgery

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HIGHLIGHTS

- Lymphedema was present in 27% of endometrial cancer patients 12–18 months after surgical staging.
- Lymphedema was associated with at least a short-term worsening of lower extremity function.
- Lymphedema was not associated with a change in global quantity of life.

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ABSTRACT

Objective. The primary aim of this study was to pilot the use of an objective measurement technique to prospectively evaluate the incidence of lower extremity lymphedema (LEL) after minimally invasive staging surgery for endometrial cancer. Secondary objectives included observation of changes in lower extremity function and quality of life in this patient population.

Methods. A prospective evaluation of LEL was performed in 97 women who underwent minimally invasive staging surgery for endometrial cancer using comparative circumferential volume measurements. Postoperative changes in lower extremity function and global quality of life were also assessed using patient-reported outcome measures.

Results. Ninety-seven patients were included for lymphedema analysis. The rate of LEL was 25% at 4–6 weeks, 19% at 6–9 months, and 27% at 12–18 months postoperatively. The presence of LEL was associated with a significant worsening from baseline Lower Extremity Functional Scale (LEFS) scores at 4–6 weeks (−27.0% vs −3.7%, $p = 0.02$) and 6–9 months (−13.0% vs 0%, $p = 0.01$). LEL was not associated with a change in patient-reported global quality of life.

Conclusions. Up to one in four women experience lymphedema following surgical staging for endometrial cancer, and its presence is associated with diminished lower extremity function. Larger, prospective trials using the objective methodology piloted in this study should better clarify risk factors and long-term outcomes of this morbidity.

1. Introduction

The incidence of endometrial cancer is steadily increasing in the United States, with an estimated 62,380 new cases diagnosed in 2018 [1]. Although endometrial cancer is a worsening healthcare burden, a majority of women are diagnosed with the disease still confined to the uterus, and stage I disease has a >90% 5-year survival rate [2]. Given the excellent survival outcomes among surgically treated patients, it is imperative that providers recognize, address and potentially prevent the long-term adverse sequelae of surgical staging.

Lower extremity lymphedema (LEL) resulting from lymph node dissection is a recognized adverse outcome of the surgical management of endometrial cancer. This morbidity can limit a patient's mobility, compromise her ability to perform daily activities, and have adverse effects on her psychological wellbeing [3–5]. However, the necessity of pelvic

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lymphadenectomy in the management of early stage endometrial cancer has become a controversial subject. Given that two major randomized trials have failed to demonstrate a survival benefit to pelvic lymphadenectomy (LND), some experts assert that it has a limited role in the treatment of early stage endometrial cancer [6,7]. Others continue to recommend LND, believing that it provides useful prognostic information and guidance regarding adjuvant therapy [8]. More recently, sentinel lymph node biopsy (SLNB) has emerged as an alternative to complete lymphadenectomy that has been hypothesized to lower the risk of LEL [9].

Although mitigating the risk of LEL is one of the primary drivers of this debate, the true incidence of LEL after endometrial cancer staging surgery is unknown. Published rates of LEL in patients who undergo lymphadenectomy for endometrial cancer range from 1% to 52% [10–13]. This wide range is likely secondary to inconsistencies in diagnosis and documentation, as well as the long period of follow-up required to adequately assess the morbidity. Salani et al. also found that patient-reported symptoms of lower limb swelling were significantly higher than patient-reported diagnoses of LEL, suggesting that this diagnosis is often under-recognized by both patients and providers [14].

The aim of this study was to pilot the use of an objective measurement technique to prospectively describe the incidence of lower-extremity lymphedema among women after minimally invasive staging surgery for endometrial cancer. We hypothesized that a substantial proportion of patients experience this morbidity. Secondary objectives included observation of changes in lower extremity function and quality of life in this patient population. Additional exploratory analysis of this prospective cohort was also performed to examine outcomes in the SLNB and LND subjects separately.

2. Materials and methods

2.1. Selection of patients

A longitudinal, prospective pilot study of women undergoing staging surgery for presumed early stage endometrial cancer was conducted by enrolling patients from September 2013 to September 2015. Inclusion criteria were: (a) older than 18 years; (b) endometrial cancer of any histologic type; (c) suitable candidate for surgery; (d) scheduled to undergo laparoscopic or robotic-assisted (RA) laparoscopic hysterectomy; and (e) no severe physical or mental comorbidity. Patients were excluded if they had known metastatic disease. Given trends during the enrollment years toward minimally invasive surgery for the management of endometrial cancer, the investigation was confined to planned laparoscopies to create a more homogenous surgical cohort. Patient demographic, clinical, surgical and pathological data were collected using a standardized abstraction form.

2.2. Study procedures

Institutional Review Board approval for the study was obtained. Consent was obtained at the preoperative visit. During the enrollment visit, baseline demographic data, baseline leg volume measurements, lower extremity function and quality of life surveys were completed. Each subject then underwent endometrial cancer staging surgery, either with conventional or robotic-assisted laparoscopy. Conversion to laparotomy was not considered an exclusion criterion. Removal of lymph nodes and technique of lymph node dissection (SLNB or LND) were left to physician discretion based on clinical criteria. Post-staging assessments, including leg volume measurement and lower extremity function and quality of life surveys, were administered at three separate measurement periods: 4–6 weeks, 6–9 months and 12–18 months postoperatively.

2.3. Assessments

2.3.1. Lymphedema measurements

The Comparative Circumferential Volume (CCV) measurement method was used to evaluate leg volume preoperatively and at 4–6 weeks, 6–9 months and 12–18 months postoperatively [15]. This method consists of measuring the circumference of each lower extremity from the level of the ankle to two centimeters below the gluteal fold at four-centimeter intervals (Fig. 1). A certified lymphedema specialist trained a single clinical research coordinator in accurate assessment using the CCV. The research coordinator then performed all measurements to ensure consistency. These measurements were used to compute total limb volume. Presence of lymphedema was defined as an increase in volume of at least 10% from preoperative measurements; this minimum is based on previously established, clinically meaningful thresholds for postoperative LEL [16]. Results were dichotomized into absent (0 to <10% excess of limb volume) or present (10% or greater limb volume change).

2.3.2. Lymphedema related-morbidity

The Lower Extremity Functional Scale (LEFS) was used to evaluate lymphedema-related morbidity after staging surgery [17]. The LEFS is a validated survey that consists of twenty questions that assess the effect of a lower limb condition on a person's ability to perform everyday tasks (Fig. 2). The cumulative score can range from 0 to 80, with a higher score indicating better lower extremity function. Median score in a healthy population is 77. A minimal clinically important difference for the broad category of lower extremity injury has been defined as a 9-point decrease [17]. The LEFS questionnaire was administered before surgery and at 4–6 weeks, 6–9 months and 12–18 months postoperatively.

2.3.3. Quality of life

The FACT-G, or the Functional Assessment of Cancer Therapy – General was used to evaluate the impact of staging surgery and of lymphedema on quality of life [18]. This survey is a validated, in-depth quality of life questionnaire frequently used in oncologic populations. The cumulative score can range from 0 to 108, with a higher score indicating better quality of life. A minimal clinically important difference in the FACT-G has been defined as approximately four points [18]. The FACT-G was administered before surgery and at 4–6 weeks, 6–9 months and 12–18 months postoperatively.

2.4. Statistical analysis

This pilot study was conducted with the primary aim of estimating the incidence of lower extremity lymphedema after endometrial cancer staging surgery. Secondary objectives included analysis of postoperative quality of life and lower extremity function. Exploratory analyses included an evaluation of the effect of LEL on patient-reported outcomes, description of outcomes in SLNB and LND cohorts, and an assessment of association between the number of lymph nodes removed and the presence of LEL.

Summary statistics were used to address the study's primary aim. For incidences, 95% exact binomial confidence intervals (CI) were estimated. Summary statistics were also performed to describe the change in lower extremity function and quality of life from baseline to postoperative measurement periods in the total study population. Fisher's exact test was used to compare the association between the level of lymphedema and SLNB or full lymphadenectomy. Wilcoxon rank sum tests were used to compare LEFS and FACT-G scores between subjects with LEL and those without LEL, and between SLNB and LND subjects. Wilcoxon rank sum tests were also used to assess associations between number of nodes removed and the presence of lymphedema. Values of $p < 0.05$ were considered significant. Statistical analyses were conducted using SAS v.9.4 software (SAS Institute, Inc., Cary NC).

Method for obtaining measurements for calculating lower-extremity lymphedema

- Ask the patient to stand or sit with both feet firmly on the ground.
- On the medial aspect of the leg measure with a ruler and record the distance from the floor to 2 cm above the middle of the medial.
malleolus. Mark this point on the patient. This determines the starting point
- Mark the same point on the contralateral leg.
- Seat patient on a chair with bottom as close to the edge as possible, or seat on a couch with the leg straight.
- Lie a ruler along the medial aspect of the leg and mark the limb at 4 cm intervals from the starting point to 2 cm below the popliteal fossa for swelling below the knee.
- Continue the marks at 4 cm intervals above the knee to 2 cm below the gluteal crease.
- With the limb in a relaxed position, measure the circumference at each mark, placing the top edge of the tape measure just below the mark.
- Note measurements above the knee in the correct section of the paper form.
- Repeat the process on the other limb. Ensure there are the same number of measurements for both legs.
- Document the position the patient was in when measurements were taken.

Fig. 1. The Comparative Circumferential Volume (CCV) measurement method.

3. Results

One hundred subjects were enrolled from September 2013 to August 2015. Three were excluded: two declined to participate after enrollment, and one was found to have disseminated disease intraoperatively; surgery was thus aborted in favor of neoadjuvant chemotherapy. Subject demographics and clinical characteristics of the entire cohort are summarized in Table 1. The mean body mass index (BMI) was 37.2 kg/m^2 (SD 16.4). Twenty-seven percent (26/97) of subjects received adjuvant radiation; of these, 50% (13/26) received brachytherapy alone. The median baseline FACT-G was 92 (range 31–108); the median baseline LEFS was 69 (range 6–80).

Surgical characteristics are summarized in Table 1. Fifty-one percent (49/97) had SLNB, 36% (35/97) full LND, and 13% (13/97) did not have lymph nodes removed. Twenty-one percent (20/97) received both SLNB and LND. The median number of lymph nodes removed was 3 (1−11) in the SLNB-only group and 19 (2–49) in the full LND group. 79 (81%) subjects completed the 4–6 week data measurement set; 63 (65%) completed the 6–9 month data set, and 55 (57%) completed the 12–18 month data set. There were no significant differences in mean age, BMI, ECOG status, histology, stage or use of radiation therapy between subjects who completed the 12–18 month measurement versus those who did not.

Table 2 demonstrates the incidence of lymphedema, defined as a >10% increase in baseline leg volume, in the total study population at each measurement period. This population includes subjects who received SLNB and LND as well as those who did not have any lymph nodes removed. Lymphedema was observed in 25% (20/79) [95% CI: 16–36%] of subjects in the 4–6 week postoperative period, 19% (12/63) [95% CI: 10–31%] in the 6–9 month period, and 27% (15/55) [95% CI: 16–41%] in the 12 to 18 month measurement period.

Changes in lower extremity function and quality of life were assessed from baseline to postoperative measurement periods in the total study population. LEFS scores significantly decreased by a mean of 9.1 points from baseline to the 4–6 week measurement period (95% CI: 5.6–12.7). This trend did not persist in the later measurement periods, and no significant differences in quality of life were observed in any of the measurement periods.

The associations between the presence of LEL and lower extremity function and quality of life changes were assessed at each measurement period. Patients with earlier onset LEL (present at the 4–6 week postoperative visit) had a 27% decrease in LEFS score at 4–6 weeks and a 13%

THE LOWER EXTREMITY FUNCTIONAL SCALE

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb Problem for which you are currently seeking attention. Please provide an answer for **each** activity.

Today, do you or would you have any difficulty at all with:

	Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
1	Any of your usual work, housework, or school activities.	0	1	2	3	4
2	Your usual hobbies, re creational or sporting activities.	0	1	2	3	4
3	Getting into or out of the bath.	0	1	2	3	4
4	Walking between rooms.	0	1	2	3	4
5	Putting on your shoes or socks.	0	1	2	3	4
6	Squatting.	0	1	2	3	4
7	Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
8	Performing light activities around your home.	0	1	2	3	4
9	Performing heavy activities around your home.	0	1	2	3	4
10	Getting into or out of a car.	0	1	2	3	4
11	Walking 2 blocks.	0	1	2	3	4
12	Walking a mile.	0	1	2	3	4
13	Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
14	Standing for 1 hour.	0	1	2	3	4
15	Sitting for 1 hour.	0	1	2	3	4
16	Running on even ground.	0	1	2	3	4
17	Running on uneven ground.	0	1	2	3	4
18	Making sharp turns while running fast.	0	1	2	3	4
19	Hopping.	0	1	2	3	4
20	Rolling over in bed.	0	1	2	3	4
	Column Totals:					

Fig. 2. Lower Extremity Functional Scale (LEFS) scale questionnaire.

Table 1
Patient demographics and clinical characteristics.

Clinical characteristics	Frequency N (%) ($n = 97$)
Age (years)	
Mean (SD)	62.7 (11.3)
BMI at time of surgery	
Mean (SD)	37.2 (16.4)
BMI < 30	26 (27)
BMI 30–35	22 (23)
BMI > 35	49 (51)
Race N (%)	
Caucasian	66 (68)
Black	26 (27)
Asian	3 (3)
Native American	1 (1)
Other	1 (1)
FIGO stage N (%)	
IA	67 (69)
IB	13 (13)
II	2 (2)
IIIA	1 (1)
IIIIC1	7 (7)
IIIIC2	3 (3)
IVB	1 (1)
N/A	3 (3)
ECOG performance status N (%)	
0	58 (60)
1	37 (38)
2	1 (1)
NR	1 (1)
Comorbidities N (%)	
Hypertension	62 (63)
Diabetes	30 (31)
CAD	6 (6)
CHF	5 (5)
Pulmonary disease	5 (5)
Type of hysterectomy N (%)	
Laparoscopic	54 (56)
Robotic	34 (35)
Converted to open	9 (9)
Radiation therapy N (%)	
Yes	26 (27)
No	71 (73)
Staging technique N (%)	
SLNB	49 (51)
LND	35 (36)
None	13 (13)
Number of lymph nodes (Median, range)	
SLNB	3 (1–11)
LND	19 (2–49)

SD: Standard deviation; BMI: body mass index; FIGO: International Federation of Gynecologic Oncologists; ECOG = Eastern Cooperative Oncology Group; SLNB: Sentinel lymph node biopsy; LND: Lymphadenectomy.

decrease at 6–9 months from their baseline score. This represents a significant difference in median LEFS score changes between patients with and without earlier-onset LEL at both the 4–6 week (−3.7% vs −27.0%, $p = 0.02$) and 6–9 month period (0.0% vs −13.0%, $p = 0.01$). The presence of LEL at the 6–9 month and 12–18 month periods was not associated with differences in lower extremity function outcome measures. Global quality of life, as measured by FACT-G, was not significantly affected by the postoperative presence of LEL at any measurement time.

Table 2
Incidence of lymphedema after endometrial cancer staging.

Volume change	Total population N (%)	LND N (%)	SLNB N (%)	Fisher's exact
4–6 weeks	$n = 79$	$n = 31$	$n = 37$	1.0
>10% increase	20 (25)	9 (29)	11 (30)	
6–9 months	$n = 63$	$n = 26$	$n = 29$	1.0
>10% increase	12 (19)	5 (19)	5 (17)	
12–18 months	$n = 55$	$n = 21$	$n = 28$	1.0
>10% increase	15 (27)	5 (24)	7 (25)	

Fisher's exact test for comparing proportions between LND and SLNB.

The objective volume change from baseline and all patient-reported outcomes were evaluated in the LND and SLNB cohorts as an exploratory analysis. There were no differences between these two cohorts in the incidence of LEL at any measurement time (Table 2). There was no difference in lower extremity function or quality of life change from baseline between the two cohorts at any measurement period (Table 3).

The presence of lymphedema in the three postoperative measurement periods was not significantly associated with the median number of pelvic or total nodes removed. A median of 4.0 total nodes and 2.0 pelvic nodes were removed in those with lymphedema at the 12–18 month measurement period, compared to a median of 5.0 total nodes and 3.5 pelvic nodes in those without lymphedema.

4. Discussion

Few prospective studies have been designed to evaluate lymphedema as a primary outcome after endometrial cancer staging [13,19]. In the current study, one in four women who underwent minimally invasive endometrial cancer staging experienced lymphedema, as defined by a leg volume change >10%, more than a year after primary surgery. The threshold of 10% increase was based upon a prior study that correlated volume change thresholds with patient-reported outcomes and found that a circumferential sum increase of ≥7% provided a clinically meaningful definition of lymphedema [16].

The previously published rates of lymphedema after endometrial cancer surgery vary too widely in the literature to have true clinical utility, with reported results ranging from one to 52%. The majority of these studies were performed in a retrospective fashion with inconsistent measurement methods [13,20,21]. The disparities among data emphasize the need for prospective investigations using both objective measures and patient-reported outcomes regarding the effect of volume change on their daily lives. Recently, preliminary results from a large, prospective study (the Lymphedema and Gynecologic Cancer (LEG) trial) showed a leg volume change of >10% in 34% of postoperative endometrial cancer patients. However, only 18% of endometrial cancer patients had LEL when using a multifactorial definition of the morbidity that included both volume change and patient-reported swelling [22].

The current study prospectively evaluated patient-reported lower limb function and quality of life in postoperative endometrial cancer patients. There was no significant change from baseline at long-term follow-up in either lower extremity function or quality of life. However, the presence of lymphedema as defined by volume change alone was significantly associated with worse lower extremity function at 4–6 weeks and 6–9 months, with a median 27% decrease at 4–6 weeks and 13% decrease in 6–9 months, compared to the 4% and 0% median LEFS score decreases in patients without LEL at these measurement periods. This change represents an increase in difficulty performing activities of daily living and a worsening of general mobility. This difference did not persist at 12–18 months, despite an increasing incidence of lymphedema at this time.

Failure to demonstrate a change in the later measurement periods may be secondary to lower subject numbers. It is also possible that no clinically meaningful difference in patient-reported function exists as patients become accustomed to the physical changes over time. It may also be that, despite some evidence to suggest 10% as a reasonable volume discrepancy, the threshold should be higher to better capture long-term clinically meaningful LEL [16]. This issue could be addressed in larger, prospective trials using measurement methodologies similar to those piloted here. No association was found between lymphedema and global quality of life, which is consistent with some previously published results [23,24]. However, the significant lower extremity function changes are evidence that LEL, as defined by volume change alone, does have at least a short-term effect on a patient's mobility and functional status.

Table 3
Percent change from baseline in survey outcomes by staging technique.

	LND				SLNB				Wilcoxon Rank Sum
LEFS	N	Median	Lower quartile	Upper quartile	N	Median	Lower quartile	Upper quartile	*p*-Value
4–6 weeks	30	−4.38	−45.16	1.67	37	−5.08	−15.07	0.00	0.8
6–9 months	26	−0.64	−9.21	3.90	28	0.00	−16.16	1.98	0.8
12–18 months	21	0.00	−12.66	12.68	28	0.00	−10.96	2.32	0.9
FACT-G	N	Median	Lower quartile	Upper quartile	N	Median	Lower quartile	Upper quartile	*p*-Value
4–6 weeks	31	−3.06	−11.21	3.83	37	0.96	−3.70	6.76	0.05
6–9 months	26	3.92	−11.30	12.74	27	2.11	−2.88	13.18	0.5
12–18 months	21	2.41	−3.19	9.38	26	6.10	−3.85	12.64	0.7

LEFS: Lower extremity functional scale; FACT-G: Functional assessment of cancer therapy-General; LND: Lymphadenectomy; SLNB: Sentinel lymph node biopsy.

The necessity and benefit of lymphadenectomy in early endometrial cancer has become a topic of controversy. In theory, because SLNB involves less extensive surgery and the removal of fewer lymph nodes than standard lymphadenectomy, it could provide a lower risk alternative for lymph node evaluation [9]. The exploratory analyses evaluated outcomes in SLNB and LND cohorts and identified no significant differences in LEL incidence, quality of life or lower extremity function between the two cohorts at any measurement period. However, the evaluation of SLNB and LND subjects as separate cohorts was an exploratory analysis that must be interpreted with caution. A post-hoc power analysis assuming a 25% incidence of LEL demonstrated a required sample size of 110 to show a 15% difference in LEL rates between SLNB and LND cohorts with a power of 0.8 and an alpha of 0.1. This pilot study was therefore not powered to detect differences between SLNB and LND cohorts.

Of note, twelve of the SLNB subjects had more than two lymph nodes removed from at least one side, and two outliers in the LND group had only two nodes removed. Lymph node counts are typically determined during gross examination of surgical specimens and are based on how many separate nodes are isolated by the surgical technician; this process is likely variable across institutions. Collection method alone can significantly affect final pathologic count of nodes, and a fair degree of inter-observer variability has been demonstrated [25,26]. These issues likely blur the distinction between the two subgroups in the current analysis. Because of the range of lymph nodes removed per surgical category, a separate exploratory analysis was performed using actual node number rather than stated node evaluation technique. Previous reports suggested that the incidence of lymphedema may be proportional to the number of lymph nodes removed, although the threshold nodal count ranges from ten to thirty-one lymph nodes [21,27]. However, the mean node count was not significantly higher in patients with lymphedema, a phenomenon observed in the LEG trial as well, suggesting that increased nodal count may not be as important a risk factor for LEL as previously hypothesized [22].

One recent trial prospectively compared rates of lymphedema between SLNB and LND in endometrial cancer patients and reported a 14-fold decreased risk of lymphedema in the SLNB group [19]. However, this difference was only reported for grade 1 lymphedema, defined as 5–10% inter-limb discrepancy and not compared to a preoperative baseline. In contrast, the current study employed the use of a preoperative baseline leg volume and used a previously defined clinically relevant volume difference of >10% [19].

The strengths of the current study include the use of objective methodology to classify lower-extremity lymphedema according to volume measurements. In addition, the presence of this volume change was correlated to clinically meaningful patient-reported outcomes. The study had several limitations. One of these was the significant attrition in measurement and survey completion over course of the study, with 97 subjects originally enrolled but only 55 (57%) completing the 12–18 month data. The high rate of attrition was likely secondary to patients who underwent preoperative evaluation and surgery at the primary institution and then chose to receive follow-up or surveillance at an associated satellite clinic where the research coordinator was not available. However, attrition bias was likely limited, as key demographic factors, disease histology and stage and incidence of radiation therapy did not differ between the subjects who completed the 12–18 month measurement and those who did not. Also, although a relationship between decreased lower extremity function and LEL was demonstrated, the use of a multicomponent definition of lymphedema requiring objective and subjective volume change and impact on quality of life would have created a more robust assessment of this morbidity. A further limitation of the study was that the subject number was too small to analyze outcomes of adjuvant treatment cohorts separately, although radiation is a known risk factor for lymphedema [20].

In conclusion, lymphedema occurs at appreciable rates in women undergoing staging surgery for endometrial cancer. Certain lower risk patients may not need lymphadenectomy, and the role of risk-stratifying algorithms has become clinically prevalent. However, imaging remains an inefficient way of assessing lymph node status in higher risk cases, and nodal evaluation may be helpful in at least some endometrial cancer patients. As demonstrated in this study, both available techniques for lymph node assessment – LND and SLNB – are accompanied by at least some risk of LEL. Considering the prevalence of this morbidity, more robust surveillance methods and management strategies should be investigated. Interestingly, no improvement in objective or subjective measurements could be detected between the SNLB and LND groups; nor was there a difference in the number of nodes removed between LEL and non-LEL groups. Larger, prospective studies should be performed to capture more definitive data comparing the lymphedema related outcomes based on technique and number of nodes removed.

Conflicts of interest

The authors report no conflict of interest relevant to the subject of this paper.

Author contributions

ML and LH developed the concept of this study. AB, LH, FV, BD, and PL enrolled patients. JE was involved in patient enrollment and completion of all outcomes measures for each patient encounter. GB and AK performed the statistical analysis. CW drafted this paper with support from ML and LH. All authors critically reviewed and revised subsequent drafts and approved of the final version as presented.

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